Breast Cancer Survival and Physical Activity, Obesity, and Weight Gain

Two recent studies provide new information on physical activity, obesity, and weight gain in relation to breast cancer survival. Michelle Holmes, M.D., Dr.P.H., of Brigham and Women's Hospital and Harvard Medical School, and colleagues analyzed data from nearly 3,000 women participating in the Nurses' Health Study (NHS) who were diagnosed with stages I, II, and III breast cancer. Women with breast cancer who engaged in physical activity equivalent to walking one or more hours per week had better survival than those who exercised less than that or not at all. The benefit was particularly apparent for women with hormone-responsive tumors. Physical activity has been linked to lower levels of circulating ovarian hormones, which may explain the relationship between physical activity and breast cancer.

In other NHS research, Candyce Kroenke, Sc.D., of the same institutions, and colleagues found that women who are overweight prior to breast cancer diagnosis, or who are lean but gain weight following diagnosis, are more likely to have their disease return or to die from it. This effect was particularly pronounced among women who had never smoked. This is the first study of obesity and breast cancer to separate smokers from nonsmokers. Maintaining a healthy weight is important to reduce the risk of breast cancer recurrence and death, report the researchers. The study was based on data on 5,204 breast cancer patients collected over 24 years. The two studies were supported by EGRP grants to Graham Colditz, M.D., Dr.P.H.

SHBG Gene Polymorphism and Breast Cancer Protective Effect

Sex hormone-binding globulin (SHBG) modulates the bioavailability of circulating sex hormones, regulating their effects on target tissues. The *SHBG* gene in breast cancer cells inhibits estradiol-induced cell proliferation and thus may influence breast cancer risk. Young Cui, M.D., of Vanderbilt University School of Medicine, and colleagues examined the association between a common functional polymorphism of the *SHBG* gene (*Asp327Asn*) and risk of breast cancer in a large population-based case-control study in Shanghai, China. The variant *Asn* allele was associated with elevated plasma *SHBG* levels and decreased risk of breast cancer in postmenopausal women (27% reduction in risk). The allele's protective effect was much stronger among postmenopausal women with low adiposity (more than 50% reduction in risk). The inverse association between the allele and breast cancer risk also was stronger for estrogen receptor-positive cancer than for estrogen receptor-negative cancer. The study included 1,106 cases and 1,180 controls. Supported by EGRP grants to Wei Zheng, Ph.D.

Search for Markers of Cancer Susceptibility

In earlier research, Qingyi Wei, M.D., Ph.D., of The University of Texas M.D. Anderson Cancer Center, and colleagues showed that increased risk of squamous cell carcinomas of the head and neck (SCCHN) is associated with reduced DNA repair capacity and reduced levels of nucleotide excision repair (NER) mRNA in lymphocytes. In a pilot case-control study, he and his team investigated expression of six core NER proteins in relation to risk of SCCHN. They developed a reverse-protein microarray assay to measure NER protein expression in lymphocytes from 57 SCCHN patients and 63 controls. In a model that included all covariates and NER proteins, only low expression of the NER protein XPF remained a significant risk factor. They concluded that XPF may be a crucial rate-limiting factor in DNA repair and that the microarray assay may be a useful tool for measuring protein markers of susceptibility to cancer. Supported by an EGRP grant to Dr. Wei.

Research Highlights

New Model for Ovarian Cancer Risk

MUC1 is a protein that is expressed in different forms by both healthy and cancerous cells. When expressed by cancerous cells, MUC1 stimulates the production of antibodies. In a case-control study of ovarian cancer, Daniel Cramer, M.D., Sc.D., of Brigham and Women's Hospital, and colleagues measured anti-MUC1 antibodies in 705 women who did not have ovarian cancer, identified events that predicted antibody production, and estimated risk for the cancer by comparing profiles of the events that generated antibodies in the women with similar events in 668 women with ovarian cancer. Factors that predicted antibody production included use of oral contraceptives and intrauterine devices, breast mastitis, bone fracture or osteoporosis, pelvic surgeries, nonuse of talc in genital hygiene, and being a current smoker. Women who had two factors leading to elevated MUC1 antibody levels were about 30 percent less likely to develop ovarian cancer than women with none or only one MUC1 antibody-promoting event. Women with five of the factors had about a 70 percent reduction in risk compared with women with none or one of them. Besides presenting a new model to explain risk factors for the cancer, the researchers speculated that the findings could lead to development of preventive vaccines for ovarian and maybe other cancers that express MUC1. Supported by an EGRP grant to Dr. Cramer.

Diet and Non-Hodgkin's Lymphoma

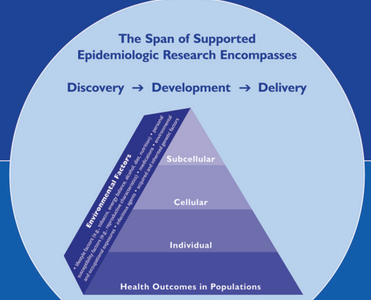
The incidence of non-Hodgkin's lymphoma (NHL) has increased rapidly worldwide in recent decades for reasons that are largely unknown. Ellen Chang, Sc.D., of the Karolinska Institutet, and colleagues examined the role of diet in the development of NHL in a population-based case-control study in Sweden. Higher intakes of dairy products and fried meat, especially red meat, were associated with increased risk of some NHL subtypes in both men and women. The odds ratio (OR) of NHL for individuals in the highest quartile of intake of dairy products to the lowest quartile was 1.5. The OR for the highest quartile of intake of fried red meat was 1.5. Higher intakes of fruits and vegetables were associated with decreased risk of NHL, particularly follicular lymphoma, among women (OR=0.3). The researchers concluded that spread of the Western diet, with its high intake of dairy products and cooked and processed meats and low intake of fruits and vegetables, could account for a moderate proportion of the worldwide increase in NHL incidence, and that dietary modifications could help prevent some of the more common subtypes of NHL. The study included 597 cases and 467 controls. Supported by an EGRP grant to Dr. Chang.

The Epidemiology and Genetics Research Program (EGRP) manages a comprehensive program of grant-supported, population-based research to increase our understanding of cancer etiology and prevention. Scientists from throughout the United States and internationally are supported.

EGRP is a rich resource for investigators . . .

EGRP Program Directors provide information, consultation, and advice about National Cancer Institute (NCI) and National Institutes of Health (NIH) funding, science policies and procedures, preparation of grant applications, and funding instruments relevant to the Program.

EGRP's research portfolio encompasses about 450 projects that are funded annually through grants and cooperative agreements.



New NCI MERIT Award Recipients

Anna-Barbara Moscicki, M.D. University of California at San Francisco: Natural History of HPV Infection to Neoplasia

Raymond Carroll, Ph.D. Texas A&M University System: Measurement Error, Nutrition, and Breast/Colon Cancer

Two EGRP grantees have received FY2005 NCI Method to Extend Research in Time (MERIT) Awards, which provide an additional 5 years of research funding. MERIT awards support investigators with Research Project Grants (R01) whose competence and productivity are distinctly superior.

Current Program Announcements

- Pilot Studies in Pancreatic Cancer (R21, R03) - PA-05-116
- Studies of Energy Balance and Cancer in Humans (R01, R21, Competitive Supplements) - PA-04-124
- Exfoliated Cells, Bioactive Food Components, and Cancer (R01, R21, R03) - PA-04-114
- Small Grants Program for Cancer Epidemiology (R03) - PAR-04-159
- Cohort Studies in Cancer Epidemiology (R01) - PAR-04-011
- Research on Malignancies in AIDS and Acquired Immune Suppression (R01, R21) - PA-04-157
- Occupational Health and Safety Research (R01) - PA-04-038
- Small Business Innovation Research and Small Business Technology Transfer Research Programs

To discuss EGRP research and funding opportunities, please consult our online staff directory at epi.grants.cancer.gov/staff.html, or telephone: (301) 496-9600.

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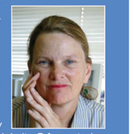
New Information on Hereditary Colorectal Cancer Risk

Noralane Lindor, M.D., of the Mayo Foundation, and colleagues studied individuals with a family pedigree suggestive of hereditary nonpolyposis colorectal cancer (HNPCC) but who lacked the characteristic DNA mismatch repair gene defect (*MMR*). They found that families without the DNA defect had a lower risk of colorectal cancer, were diagnosed at a later age, and had a lower incidence of other cancers associated with HNPCC than did families with the defect. About 60 percent of families that meet criteria for a certain type of HNPCC, Amsterdam-I (AC-I), have an abnormality in a DNA *MMR* gene. Cancer incidence in AC-I families with *MMR* gene mutations is high, but the incidence for individuals in AC-I families without evidence of an *MMR* defect has been unknown. In counseling families with AC-I, clinicians now can provide more accurate and lower-risk information using these new data in combination with the specific family history, report the researchers. The study included 161 families who met the AC-I criteria; most of the families were from the EGRP-funded Colon Cancer Family Registry (C-CFR). Supported by EGRP grants for the Registry, of which Dr. Lindor is one principal investigator.

Chickenpox and Brain Cancer



In past research, Margaret Wrensch, Ph.D., of the University of California at San Francisco, and colleagues unexpectedly found that adults with gliomas were less likely than controls to have a history of chickenpox and shingles and to have immunoglobulin G antibodies for varicella-zoster virus, the cause of these conditions. In new research with a different study population, she and her research team investigated whether history of varicella-zoster virus infections, or immunity to the virus or to other herpesviruses, is associated with risk for glioma. They found that patients with glioma, particularly those with glioblastoma multiforme, were less likely to report a history of chickenpox and had significantly lower levels of immunoglobulin G for varicella-zoster virus than controls. Glioblastoma multiforme is the most common and aggressive type of primary brain tumor. No significant differences were noted between cases and controls for positivity to three other herpesviruses, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus. The study included 229 adults with glioma and 289 controls participating in the San Francisco Bay Area Adult Glioma Study. The researchers recommend that cohort studies be conducted to clarify the nature of the association between immunity to and/or clinical manifestations of varicella-zoster virus and glioblastoma. Supported by an EGRP grant to Dr. Wrensch.

Research Highlights

P450 Polymorphism and Prostate Cancer in African Americans

Members of the cytochrome P450 3A subfamily of enzymes are involved in steroid hormone metabolism. Angie Stone, B.S., of the National Center for Toxicological Research, and colleagues investigated the association between the *CYP3A43*3* genotype and risk of prostate cancer in African Americans and Caucasians. Their findings suggest that the *CYP3A43 Pro*^{340} *Ala* polymorphism contributes to prostate cancer risk in African Americans. They found a 3-fold increased risk of prostate cancer among men with the *CYP3A43-Ala/Ala* genotype compared with men with the *CYP3A43-Pro/Pro* genotype when analyzing data on all study participants. The *CYP3A43-Ala/Ala* genotype polymorphism was more frequently found in African Americans than in Caucasians (45% versus 13%), and African Americans with the *CYP3A43-Ala/Ala* genotype had a 2.6-fold increased risk of prostate cancer. This is one of the first case-control studies to associate polymorphisms in the *CYP3A43* gene with prostate cancer susceptibility. It included 124 African Americans and 358 Caucasians with the cancer and 167 African-American and 319 Caucasian controls. Supported by an EGRP grant to Nicholas Lang, M.D., of Central Arkansas Veteran's Health Care System and Arkansas Cancer Research Center.

Statins and Prostate Cancer Risk

The longer men take cholesterol-lowering drugs such as statins, the far less likely they are to develop advanced prostate cancer, according to findings by Elizabeth Platz, Sc.D., M.P.H., of Johns Hopkins University, and colleagues. They tracked use of cholesterol-lowering drugs and diagnosis of prostate cancer among 34,428 men participating in the Health Professionals Follow-up Study (HPFS) and followed for more than a decade. Men who used these medications had half the risk of advanced prostate cancer and a third of the risk of metastatic or fatal prostate cancer, compared with men who did not use cholesterol-lowering drugs. Risk of advanced prostate cancer fell with increasing duration of use of the drugs. Use of cholesterol-lowering drugs did not have any influence on prostate cancer confined within the organ. The researchers believe that most of the protective effect comes from statins because by the year 2000 more than 90 percent of the men who reported using cholesterol-lowering drugs said that they were using statins. It is not known whether the apparent benefit of statins is due to their cholesterol-lowering effect or their other properties. Supported by an EGRP grant to Edward Giovannuci, M.D., Sc.D., of Harvard School of Public Health.

HPV Reactivation in HIV-Positive Women

For the first time, researchers have strong evidence that the virus that causes cervical cancer, human papillomavirus (HPV), can be reactivated after being undetectable, which is especially likely in women with impaired immunity due to HIV infection as well as other causes. These findings have major implications for HIV-positive women and others with poor immune status, report Howard Strickler, Ph.D., of Albert Einstein College of Medicine of Yeshiva University, and colleagues. The study is based on data from the Women's Interagency HIV Study (WIHS), a prospective cohort of more than 2,500 HIV-positive and HIV-negative women. The data suggest that undetectable HPV infections become active much more frequently in HIV-positive women, which may help explain the high rates of HPV infection in these women. For HIV-positive women, the CD4+ cell count in combination with HIV RNA levels appeared to have a significant association with incident detection of HPV, some of the association possibly reflecting HPV reactivation in sexually inactive women. Although weakened immune status due to HIV had a major effect on allowing HPV infections to develop, HIV had a relatively modest effect on HPV persistence, a necessity for cervical cancer to occur. This finding may help explain why cervical cancer rates have not reached more epidemic proportions in HIV-positive women. Supported by an EGRP grant to Dr. Strickler.